REMARKS

I. Rejection under 35 U.S.C. § 112

Claims 1, 6, 11, 43-45, 47-52, 54, 59-60, 75-76, 97, 109, 119-20, 124-26, 151,157, 161-66, 167, 168-170, 184, 191 and 205 (new) are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The Examiner stated the following:

> The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Enablement was considered in view of the *Wands* factors (MPEP 2164.01(a)) and Applicants' response to each factor is discussed individually below.
>
> Nature of the Invention. A brief description was given by the Examiner regarding the claimed invention. While no argument was presented under this *Wands* factor by the Examiner, Applicants makes a point to demonstrate which claims are considered dependent claims.
>
> State of the prior art. The Examiner reviewed what was known in the prior art, in particular, what was disclosed by Smyth et al (2002). In response, Applicants point out that "intermediary metabolites" are considered to be the products of enzymatic processes in a mammalian system as it is defined in US Patent Application 10/375, 906. In contrast, Applicants argue that Smyth et at describes an "artificial ligand".
>
> Applicants' arguments are considered but not found to be persuasive. While Applicants provide statements from the '906 application, only a partial disclosure is provided. Intermediary metabolites are described completely in the following statements in same paragraph of the same application as presented by the Applicants:
>
> "In the present invention, metabolites or intermediary

> metabolites are considered to be products of enzymatic processes in a mammalian system. Such processes can include enzymatic synthesis, enzymatic degradation, enzymatic modification. Such products may include but not be limited to lipids, saccharides, glycoplipids, lipoproteins, and glycoproteins other than antibodies, cytokines or hormones. Such products may be produced in a mammalian system, a non-mammalian system, produced through recombinant DNA, produced in vitro, created synthetically or any combination thereof."
>
> Given the above disclosure demonstrates that intermediary metabolites can refer to a "non-mammalian system" as well as one "created synthetically" this rejection is maintained. It is noted here that Applicants appear to invite the Examiner to read limitation into the claims. The Examiner will not accept this invitation.

Applicants believe there is a misunderstanding regarding the definition of an intermediary metabolite in the '906 application. Applicants previously defined intermediary metabolites in the '906 application as being the products of enzymatic processes in a mammalian system. This description states that intermediary metabolites are substances that are found in a mammalian cell due to the in situ synthesis of such a product. As such, they may be present in a mammalian cell due to synthesis in the cell from other components or in contrast, they may represent a degradation process where a native compound is broken down in a mammalian cell to generate other compounds. The emphasis is that these compounds are native to mammalian cells and could be identified as being present in such a cell through a series of isolation or identification steps commonly used in analytical techniques. In the specification of the present invention, the first sentence of the Summary of the Invention states: "This invention relates to the use of a naturally occurring mammalian intermediary metabolite or T cell receptor ligand...." The phrase "Such products may be produced in a mammalian system, a non-mammalian system, produced through recombinant DNA, produced in vitro, created synthetically or any combination thereof" is being used by the Examiner as the definition of a mammalian intermediary metabolite. The Examiner also uses this sentence to expand the definition of an intermediary

metabolite in the claims: that a substance that fulfills any one of the descriptions above is identified as an "intermediary metabolite". Applicants respectfully believe that this passage is not being used appropriately because if an intermediary metabolite must only be covered by one of these terms, it renders the true definition found in the first sentence of the Summary of Invention meaningless. Appropriate use is only achieved when there is recognition that the true definition is the definition in and of itself whereas the sentence referring to "may be produced" is referring to ways that a compound that is encompassed by the true definition may be provided for administration to a subject. Thus, if a compound that is found within mammalian cells is intended for use as a therapeutic agent, it may be isolated from either a mammalian source, or a non-mammalian source, if such a source is available. However, if the source is non-mammalian, the intermediary metabolite must be identical to one isolated from a mammalian source. Similarly, the compound may be obtained through recombinant DNA techniques, produced biologically through one or more *in vitro* reactions or it may be synthesized through an appropriate series of chemical steps. Irrespective of the compound's origins, the identity of the compound must still correspond to a compound that is a metabolic product of a mammalian cell.

As such, a mammalian intermediary metabolite would be recognized as a normal product regardless of whether it was isolated from a mammalian or non-mammalian source and after administration, it would be reacted with and metabolized as if it was made in the cell itself (i.e., in a mammalian source). On the other hand, a substance such as α-GalCer (α-glucosylcerebroside) is recognized as being foreign to a mammal. Applicants would like to point out that the existence of this substance was known at the time of the filing of the '960 application and is described in the last paragraph of the Background of the Invention section as follows: "Stimulation of immune system has also been seen by introduction of α-glucosylcerebroside (Kawano et al., 1997 Science 278; 1626-1629, Burdin et al., 1998 J. Immunol 161; 3271-3281). This is apparently an antigen-induced series of events since this compound was isolated from a marine

sponge and is not a compound normally found in mammalian cells. It can be seen from this passage that the existence of the alpha compound was acknowledged and was specifically identified as not being a mammalian intermediary metabolite. The Smyth et al. reference describes KRN7000 as: "a marine-sponge glycolipid with a novel α-GalCer structure" thereby emphasizing its derivation from a non-mammalian cell, and its uniqueness in having an alpha linkage between the sugar and lipid moieties.

Further support for the meaning of a mammalian intermediary metabolite is found in the claim language and descriptions of the '906 application through use of the phrase "raise the level" (of the intermediary metabolite). In order to raise a level, it is implied that there is already at least some level of the metabolite present in the cells prior to treatment. Two means are essentially given for increasing the level: 1) addition of the metabolite (or a precursor) from an exogenous source; or 2) providing a treatment that increases the endogenous levels by either increasing synthesis or decreasing breakdown. In the former case this would not be referred to as "raising the level" if there wasn't some particular level already present in the cells prior to administration and with regard to the latter method, these methods would only have application if the compound was already being produced in these cells prior to a treatment that increases synthesis or decreases breakdown.

As such, Applicants' response to the previous Office Action was not intended to "invite the examiner to read limitations into the claims" but rather to point out the limitations that are intrinsic due to the definition given in the specification, and to also respectfully caution the Examiner from eliminating limitations that are present in the claims by definitions that expressly provide such limitations in the specification.

In an effort to create a clearer distinction between the claims of the present invention and the prior art, Applicants have amended the claims to replace "intermediary metabolite" with "mammalian intermediary metabolite". "Mammalian intermediary

metabolite" was incorporated in many of the claims in '906 application. With these amendments, the nature of these compounds is more clearly defined as substances that would be a normal constituent of mammalian cells, keeping in mind that although such a substance is required to be a constituent of a mammalian cell, the source is not required to be a mammalian cell when administered to cells or to a subject.

> Breadth of the Claims. The Examiner has pointed out that the claims are broadly written, encompassing any and all diseases, mammals and intermediary metabolites. Further, the claims are not drawn to any type of NKT cells. The Examiner maintains that this analysis is accurate and properly describes the "Breadth of the Claims". Applicants have responded in stating that the claims have been limited to "mammalian intermediary metabolites". The Examiner invites the Applicants to read the claims of the instant application again for this is simply not true. Further, as shown above, the '906 application does not support such an assertion as argued by Applicants.

Regarding the Examiner's comments on the Breadth of the Claims, Applicants respond that they have amended the claims to include the nature of the diseases by the addition of the limitation "wherein an inflammatory immune response contributes to the pathogenesis of said disease". This limits the particular diseases that would be used with the current invention since many diseases do not involve an inflammatory response and for most diseases that do involve an inflammatory response, this response is part of the curative process rather than the pathogenesis.

Applicants have further limited the breadth of the claims to recite that the mammalian intermediary metabolite comprises a lipid or glycolipid.

Regarding the Examiner's comments "encompassing any and all ... mammals", Applicants believe that there is sufficient similarity between metabolic processes in various mammals that both the terms "mammalian intermediary metabolite" and

"disease in a mammalian subject" are appropriate. It is well known that mammals as a class are considered to be similar enough to each other that animals are commonly used as models for a wide variety of human diseases. Furthermore, it has been a basic assumption that development of effective treatments in such models is for application with treatments of humans. Moreover, most intermediary metabolites in mammals are shared across a spectrum of species. This concept is best summarized by Nobel Prize winner Jacob Monod who stated: "What is true for E. coli is true for an elephant". Monod tried to explain the concept that the basic processes of life are carried out in the same way even in cells that are that extremely dissimilar to each other. In the present invention, we are speaking of intermediary metabolites, and compounds that are intermediary metabolites in one mammalian species are exceedingly likely to be found in even distantly related mammalian species.

> Working Examples. The working examples do not sufficiently support the claimed invention; they do not provide any correlation between any and all intermediary metabolites and the successful treatment of any and all diseases as claimed. In response, Applicants have invited the Examiner to read the following limitation into the claims "a defect in the immune response of the subjects to the disease". The Examiner will not accept this invitation. Additionally, Applicants have referred to two issued US Patents. However, the underlying strategies applied to other patents are not relevant and will not be discussed further.

Regarding the Examiner's comments on "Working Examples", as stated above, Applicants are restricting the claims to diseases where an inflammatory immune response contributes to the pathogenesis of the disease and as such, do not encompass "any and all diseases". The specification discloses examples where at least three different diseases with this feature were tested: an animal model where treatment with Concanavalin A leads to hepatic inflammation; an animal model where treatment with TNBS leads to colitis; and leptin deficient mice that serve as a model for NASH (non-alcoholic steatohapatitis). Thus, although these diseases are derived by

completely different means, they share the common feature of an inflammatory process responsible for the symptoms of the disease, and treatment with a mammalian intermediary metabolite alleviated these symptoms.

> Guidance in the Specification. The specification provides little guidance regarding the practice of the methods as claimed. There is no specific guidance regarding the treatment of all diseases via administration of all possible intermediary metabolites. Further, no guidance is disclosed which refers to either the CD1d molecule or the NTK cells as claimed. The Examiner maintains that this analysis is accurate.
>
> Applicants state "there are usually standard parameters that are commonly used to assess the presence or stage of a disease process". Beyond this sentence, Applicants fail to demonstrate that all standard parameters for all diseases are indeed known and that one of ordinary skill in the art can successfully use the claimed methods without additional experimentation. It is further noted that Applicant cite the following without any support: "Variations in the particular compounds used by such a practitioner can also be expanded from the specific ones cited in the working example with reasonable expectations of success".

With reference to the section in the Office Action addressing "Guidance in the Specification", as previously shown above, Applicants are restricting the claims to diseases where an inflammatory immune response contributes to the pathogenesis of the disease and as such, "treatment of all diseases" is not at issue. Identification of a disease as having an immune pathogenesis component typically involves measurement of parameters involved in inflammatory processes and as such, the particular markers that deviate from normal levels are known to those skilled in the art. As such, if a particular disease that involves inflammatory immune responses is the subject of interest, relevant immune parameters associated with that disease are already known to the practitioner before any experimentation is initiated, since this would have been described in the art as part of the process of characterizing the disease as having

inflammatory immune responses. Thus, effects of administration of a mammalian intermediary metabolite with regard to a particular disease can be carried out without undue experimentation. In addition, the involvement (or lack of involvement) of NKT cells will most often be known with regard to any such disease. In the absence of such knowledge, standard methods that have been used to evaluate the role of NKT cells may be employed without resorting to a level that would be construed as undue experimentation. In a similar fashion, the effects of an intermediary metabolite on CD1d molecules is again a matter of standard experimentation.

The Office Action states that "Applicants fail to demonstrate that all standard parameters for all known diseases are indeed known and that one of ordinary skill in the art can successfully use the claimed methods without additional experimentation." With regard to the first part, we wish to point out that it not a requirement for the practice of the invention that **all** parameters be known for **all** diseases. As noted above, the claims have been restricted to diseases that involve inflammatory immune responses and as such some immune parameters must have been previously measured for a disease to be so characterized. Thus, it is not necessary to identify each and every parameter that is associated with a particular disease and ones that already been described for the disease should provide a basis for testing the effectiveness of a compound in treatment of the disease. In many circumstances, one parameter is sufficient to test the effectiveness of a treatment on a disease. With regard to the second part, we certainly would not expect that a practitioner will be able to use the present invention "without additional experimentation" but we do contend that they will be able to do so without an undue level of experimentation.

> Predictability of the art. The Examiner has noted that there is no way one could predict the therapeutic effect of any and all intermediary metabolites for the treatment of any and all diseases as claimed.

In response, Applicant state the following:

"Applicants have disclosed an invention that can be used to alter the immune response of an individual to a disease and believe that if it is understood that the invention is being applied to diseases with an immune factor being an essential part of the disease process, it is likely that they may benefit from the present invention. A disease that does not involve an immune aspect would not be a disease of the present invention and would be viewed as unlikely to achieve any benefit from the present invention. Also, it would be known to the skilled practitioner, how much of a factor the immune response contributes towards the disease process. This is a factor that would be understood to directly correlate with the likelihood of therapeutic relief. With regard to the particular intermediary metabolites, the particular ones used in the examples are more likely to be immediately applicable, while a reasoned investigation of similar molecules can be carried out to expand the available repertoire of available reagents. Application of the present invention to other diseases and with other reagents should not require undue experimentation."

From the above recitation, it appears that Applicants are limiting the disease of the claimed invention to those "diseases with an immune factor being an essential part of the disease process". It is not clear, however, if any such disease that does not fit into the given category exists. This not a persuasive argument and the rejection is maintained.

With regard to the section on the "Predictability of the art", we believe that this was appropriately addressed in the section that the Office Action cited. However, it appears that the Office Action deemed this to be an unpersuasive argument on the basis that "it is not clear, however, if any such disease that does not fit into the given category exists." We wish to point out that a requirement that a disease involve the immune system is not a phantom limitation that still allows the claim to describe any and all disease. To clarify this point, we have added amended the claims with the language "wherein an inflammatory immune response contributes to the pathogenesis of said disease". As we have stated previously, many diseases do not involve an inflammatory response at all and for most diseases that involve an inflammatory response, this

response is part of the curative process rather than the pathogenesis. The present invention discloses treatment for specific diseases where pathogenesis is the causative agent in the disease. There are few diseases where induction of an immune response either causes or augments debilitating symptoms. When there is disease, the immune system usually acts to eliminate the disease-causing factor and/or ameliorate its effects. If Applicants' cited response is read in light of this perspective (and understood as describing a limited groups of diseases) the common factor that is being treated in these illnesses provides predictability of application of the present invention to a number of different diseases for which pathogenesis is caused or augmented by an immune response in the subject.

> Amount of experimentation necessary. It would require years of further research to develop effective therapy for any disease. Applicants have not responded to this and have instead shifted the argument which will not be further discussed.

Applicants respectfully disagree with the Examiners' statement that "It would require years of further research to develop further effective therapy for any disease." Unamended Claim 1 reads as follows: "A method for the treatment of a disease in a mammalian subject comprising administering to said subject an effective amount of an intermediary metabolite." As Applicants previously explained, the specification disclosed working examples where three different diseases (hepatic inflammation, colitis and non-alcoholic steatohepatitis) in mammalian subjects were successfully treated with an intermediary metabolite that lead to an abrogation of certain symptoms associated with inflammatory responses which contributed to the pathology of their diseases. Therefore, even without taking into consideration the new claim amendments, Applicants have provided three clear examples which apply the methods of the present invention that are encompassed by the language and terms of Claim 1. Applicants respond that it is quite unrealistic to state that it would take years to practice the present invention when three separate working examples have actually been disclosed. Furthermore, as described above, Applicants have included limitations in Claim 1

thereby showing that the diseases are restricted to ones that have pathology contributed by immune reactivity and that the mammalian intermediary metabolites used for treatment of the disease are limited to lipids and glycolipids. These limitations are part of the exemplifications of the three disease models described above and as such, create a closer association between the claimed method and the disclosed examples.

In conclusion, Applicants believe that the disclosures provided in the specification of the present invention not only do not necessitate undue experimentation, but also severely limit the requirement of any additional experimentation to carry out the claimed invention.

II. Rejections under 35 U.S.C. § 102

Claims 1, 11, 43, 54, 59-60, 75, 97, 109, 119-120, 124-126, 157, 168-170, 184, 205 (new) are rejected under 35 U.S.C. 102(b) as being anticipated by Taniguchi et al. The Examiner stated the following:

> This prior art reference teaches a treatment method in which glycosylceramides and derivatives are used as the active ingredients in activating NKT cells; this method serves as remedies for diseases and disorders, including ulcerative colitis (whole document). The structure of glucocerebroside is disclosed on page 3. Further, "antigen presenting cells treated with KRN 7000 showed a marked stimulative effect on Va24+ NKT cell proliferation in a manner dependent on the number of antigen-presenting cells" (page 18, lines 57-58, also see Figure 9 on page 36). Taniguchi et al disclose the use of autologous antigens in the following quote "an autologous mixed leukocyte reaction (MLR) was performed using these antigen-presenting cells as stimulator cells and autologous peripheral blood mononuclear cells asresponder cells" (page 18, paragraph 98). Given that Taniguchi et al meet all of the limitations of the above, these claims are rejected.
>
> In response, Applicants invite the Examiner to read limitations into the claims. The Examiner respectfully declines. The argument that the intermediary metabolites are mammalian is

> presented again and Applicants point to '906 Application to support the argument. As stated above, Applicants only provide a partial disclosure when in reality the intermediary metabolite can be both "non-mammalian" and "created synthetically". Further, Applicant points out that Taniguchi et al teach using an alpha linkage between the sugar and the lipid and that such a linkage is not considered a mammalian intermediary metabolite. The Examiner would like to remind the Applicant that claim 119 is drawn to a method using an intermediary metabolite, more specifically, a conjugated biomolecule. Thus, it appears that the Applicant is contradicting the claimed invention.

Applicants believe that Taniguchi et al. is not an anticipating reference. This prior art reference focuses on the use of KRN7000, which is not a mammalian intermediary metabolite. Applicants have provided numerous arguments to support the requirement of a mammalian intermediary metabolite. As Applicants have already stated, they are not inviting the Examiner to read limitations into the claims but are only retaining a limitation that is described in a definition provided in the specification. The present invention always requires the use of an intermediary metabolite that is found in a mammalian cell. If the source of the intermediary metabolite happens to be non-mammalian, it still must be identical to the mammalian intermediary metabolite. The terms "non-mammalian" and "synthetic" are only applicable to a provision of a compound and not part of the definition of the compound. With regard to claim 119, the claim is dependent on Claim 1 and as such, the compound must still be a mammalian intermediary metabolite.

III. **Rejections under 35 U.S.C. § 103**

A. Claims 1, 6, 11, 43-45, 49-52, 59-60, 97, 119, 124 and 161-167 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vliet et al (1999) and Taniguchi. The Examiner stated the following:

Vliet et al discloses a method in which NKT B cells isolated from human donors are treated with KRN7000 in culture (see entire document). The alteration in cytokine profiles are shown in Tables 1 and 2 demonstrating both an upregulation and a downregulation of specific NKT cell functions. More specifically, the Table "1 reveal an upregulation of both pro-inflammatory IFN- gamma and anti-inflammatory IL-4 expression, thus, leading to a change in the Thl/Th2 balance

Vliet et al does not teach a method for the treatment of colitis in a mammalian subject with intraperitoneally administration of intermediary metabolites. Taniguchi teaches a method in which NKT cell-activating agents, including galatosylceramides or glucosylceramides, are used for therapeutic agents for diseases, including ulcerative colitis (see whole document, including pages 2 and 3). Further, this prior art reference teaches intraperitoneal administration of intermediary metabolites (see page 9, paragraph 39) comprising glucocerebroside and many of its derivatives (see pages 3-6). It would have been obvious to one of ordinary skill in the art to modify the methods taught by Vliet et al and Taniguchi et al in order to alter the cytokine responses via intraperitoneal administration of an intermediary metabolite to treat mammalian disease.

One would have motivated to do so, given the suggestion by Vliet et al, because KRN7000 can be recognized by NK T-cells and trigger cytokine release and thus, "be a useful agent in the modulation of immune responses" (see Discussion). There would have been a reasonable expectation of success, given the knowledge that intermediary metabolites are already administered for mammalian treatment, for example, the "a glucosylceramide structure protects the body from radiation" as well as "increases the number of platelets and leukocytes" (Taniguchi et al, see paragraph 8). Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Even though the Vliet reference is introduced, Applicants apply the previous arguments regarding the Taniguchi reference here as well.

B. Claim 191 is rejected under 35 U.S.C. 103(a) as being unpatentable over Vliet et al (1999), Taniguchi and Connolly and Cunningham (2000). The Examiner stated the following:

> As mentioned above, Vliet et al and Taniguchi combined teach a method for the treatment of colitis in a mammalian subject with intraperitoneally administration of intermediary metabolites. These references do not disclose food and/or water deprivation prior to administration of intermediary metabolites. This practice is, however, commonly taught in the prior art by many references including that by Connolly and Cunningham. It would have obvious to one of ordinary skill in the art to modify the methods taught by Vliet et al, Taniguchi and Connolly and Cunningham to incorporate fasting prior to the administration of intermediary metabolites. One would have been motivated to do so, given the suggestion by Connolly and Cunningham, in order to minimize the volume and increase the p11 of the gastric contents. There would have been a reasonable expectation of success, given this practice has been advised since the late 19th century (see Connolly and Cunningham). Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

The inclusion of the Connolly and Cunningham references does not cure the deficiencies of the Vliet and Taniguchi references, since neither of these references disclose the use of mammalian intermediary metabolites. Secondly, Applicants would like to point out that fasting in Connolly and Cunningham is presented in a very specific context: prior to the application of anesthesia. The use of anesthesia is not required, suggested or even contemplated in the practice of the methods of the present invention. The use of fasting in the context of Claim 191 is only a description of a means of increasing the effectiveness of the methods of the present invention.

IV. **Double Patenting**

Claims 1, 6, 11, 43-45, 59-60, 97, 119-120, 124-125, 151, 157, 165-166 and 168-169 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 and 10 of copending Application No. 10/375, 906. The Examiner stated the following:

> Although the conflicting claims are not identical, they are not patentably distinct from each other because the method steps in treating a disease in a mammalian subject are identical.
>
> This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants have included a Terminal Disclaimer to address the nonstatutory obviousness-type double patenting rejection.

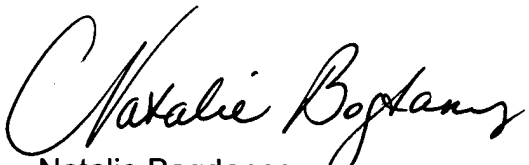
SUMMARY

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejections of record and further examination of the amended claims. These claim amendments have not resulted in the addition of new matter. Early and favorable action is respectfully requested.

No other fee or fees are believed due in connection with this paper. In the event that any fee or fees are due, however, the United States Patent and Trademark Office is hereby authorized to charge any such fee or fees to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney requests that she be contacted at the number provided below.

Respectfully submitted,



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EXAMINER	
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ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
07/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.	Applicant(s)	
10/675,980	IIAN ET AL.	
Examiner	**Art Unit**	
Michelle Horning	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *2-5, 7-10, 12-42, 46, 53, 55-58, 61-74, 77-96, 98-108, 110-118, 121-123, 129-150, 154-156, 158-160, 171-177, 183, 185, 187, 189, 190, 197, 198 and 200-202* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 6, 11, 43-45, 47-52, 54, 59-60, 75-76, 97, 109, 119-120, 124-126, 151, 157, 161-170, 184, 191 and 205* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is responsive to communication filed 5/1/2007. The status of the claims is as follows: claims 1, 6, 11, 43-45, 47-52, 54, 59-60, 75-76, 97, 109, 119-120, 124-126, 151, 157, 161-170, 184, 191 and 205 are under current examination, claims 127-127, 152-153, 178-182, 186, 188, 192-196, 199 and 203-204 have been canceled and claims 2-5, 7-10, 12-42, 46, 53, 55-58, 61-74, 77-96, 98-108, 110-118, 121-123, 129-150, 154-156, 158-160, 171-177, 183, 185, 187, 189, 190, 197, 198 and 200-202 are withdrawn from examination because they are drawn to non-elected inventions.

Withdrawn Objection and Rejection

The following objection or rejection has been withdrawn due to a mistake by the Examiner or claim amendments:

1. Objection to the Specification; and

2. 35 USC 112, 2nd paragraph.

Information Disclosure Statement

Additionally, the Examiner has considered all IDS's in full.

Claim Rejections - 35 USC § 112-MAINTAINED

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6, 11, 43-45, 47-52, 54, 59-60, 75-76, 97, 109, 119-120, 124-126, 157, 161-166, 168-169,184, 191 and 205 (new) are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Enablement was considered in view of the *Wands* factors (MPEP 2164.01(a)) and Applicants' response to each factor is discussed individually below.

Nature of the Invention. A brief description was given by the Examiner regarding the claimed invention. While no argument was presented under this *Wands* factor by the Examiner, Applicants makes a point to demonstrate which claims are considered dependent claims.

State of the prior art. The Examiner reviewed what was known in the prior art, in particular, what was disclosed by Smyth et al (2002). In response, Applicants point out that "intermediary metabolites" are considered to be the products of enzymatic processes in a mammalian system as it is defined in US Patent Application 10/375, 906. In contrast, Applicants argue that Smyth et al describes an "artificial ligand".

Applicants' arguments are considered but not found to be persuasive. While Applicants provide statements from the '906 application, only a partial disclosure is provided. Intermediary metabolites are described completely in the following statements in same paragraph of the same application as presented by the Applicants:

"In the present invention, metabolites or intermediary metabolites are considered to be products of enzymatic processes in a mammalian system. Such processes can include enzymatic synthesis, enzymatic degradation, enzymatic modification. Such products may include but not be limited to lipids, saccharides, glycoplipids, lipoproteins, and glycoproteins other than antibodies, cytokines or hormones. Such products may be produced in a mammalian system, a non-mammalian system, produced through recombinant DNA, produced in vitro, created synthetically or any combination thereof."

Given the above disclosure demonstrates that intermediary metabolites can refer to a "non-mammalian system" as well as one "created synthetically", this rejection is maintained. It is noted here that Applicants appear to invite the Examiner to read limitation into the claims. The Examiner will not accept this invitation.

Breadth of the Claims. The Examiner has pointed out that the claims are broadly written, encompassing any and all diseases, mammals and intermediary metabolites. Further, the claims are not drawn to any type of NKT cells. The Examiner maintains that this analysis is accurate and properly describes the "Breadth of the Claims". Applicants have responded in stating that the claims have been limited to "mammalian intermediary metabolites". The Examiner invites the Applicants to read the claims of the instant application again for this is simply not true. Further, as shown above, the '906 application does not support such an assertion as argued by Applicants.

Working Examples. The working examples do not sufficiently support the claimed invention; they do not provide any correlation between any and all intermediary metabolites and the successful treatment of any and all diseases as claimed. In

response, Applicants have invited the Examiner to read the following limitation into the claims "a defect in the immune response of the subjects to the disease". The Examiner will not accept this invitation. Additionally, Applicants have referred to two issued US Patents. However, the underlying strategies applied to other patents are not relevant and will not be discussed further.

Guidance in the Specification. The specification provides little guidance regarding the practice of the methods as claimed. There is no specific guidance regarding the treatment of all diseases via administration of all possible intermediary metabolites. Further, no guidance is disclosed which refers to either the CD1d molecule or the NTK cells as claimed. The Examiner maintains that this analysis is accurate.

Applicants state "there are usually standard parameters that are commonly used to assess the presence or stage of a disease process". Beyond this sentence, Applicants fail to demonstrate that all standard parameters for all diseases are indeed known and that one of ordinary skill in the art can successfully use the claimed methods without additional experimentation. It is further noted that Applicant cite the following without any support: "Variations in the particular compounds used by such a practitioner can also be expanded from the specific ones cited in the working example with reasonable expectations of success".

Predictability of the art. The Examiner has noted that there is no way one could predict the therapeutic effect of any and all intermediary metabolites for the treatment of any and all diseases as claimed.

In response, Applicant state the following:

"Applicants have disclosed an invention that can be used to alter the immune response of an individual to a disease and believe that if it is understood that the invention is being applied to diseases with an immune factor being an essential part of the disease process, it is likely that they may benefit from the present invention. A disease that does not involve an immune aspect would not be a disease of the present invention and would be viewed as unlikely to achieve any benefit from the present invention. Also, it would be known to the skilled practitioner, how much of a factor the immune response contributes towards the disease process. This is a factor that would be understood to directly correlate with the likelihood of therapeutic relief. With regard to the particular intermediary metabolites, the particular ones used in the examples are more likely to be immediately applicable, while a reasoned investigation of similar molecules can be carried out to expand the available repertoire of available reagents. Application of the present invention to other diseases and with other reagents should not require undue experimentation."

From the above recitation, it appears that Applicants are limiting the disease of the claimed invention to those "diseases with an immune factor being an essential part of the disease process". It is not clear, however, if any such disease that does not fit into the given category exists. This not a persuasive argument and the rejection is maintained.

Amount of experimentation necessary. It would require years of further research to develop effective therapy for any disease. Applicants have not responded to this and have instead shifted the argument which will not be further discussed.

Claim Rejections - 35 USC § 102-MAINTAINED

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 11, 43, 54, 59-60, 75, 97, 109, 119-120, 124-126, 157, 168-170, 184, 205 (new) are rejected under 35 U.S.C. 102(b) as being anticipated by Taniguchi et al. This prior art reference teaches a treatment method in which glycosylceramides and derivatives are used as the active ingredients in activating NKT cells; this method serves as remedies for diseases and disorders, including ulcerative colitis (whole document). The structure of glucocerebroside is disclosed on page 3. Further, "antigen presenting cells treated with KRN 7000 showed a marked stimulative effect on Va24+ NKT cell proliferation in a manner dependent on the number of antigen-presenting cells" (page 18, lines 57-58, also see Figure 9 on page 36). Taniguchi et al disclose the use of autologous antigens in the following quote "an autologous mixed leukocyte reaction (MLR) was performed using these antigen-presenting cells as stimulator cells and autologous peripheral blood mononuclear cells asresponder cells" (page 18, paragraph

98). Given that Taniguchi et al meet all of the limitations of the above, these claims are rejected.

In response, Applicants invite the Examiner to read limitations into the claims. The Examiner respectfully declines. The argument that the intermediary metabolites are mammalian is presented again and Applicants point to '906 Application to support the argument. As stated above, Applicants only provide a partial disclosure when in reality the intermediary metabolite can be both "non-mammalian" and "created synthetically". Further, Applicant points out that Taniguchi et al teach using an alpha linkage between the sugar and the lipid and that such a linkage is not considered a mammalian intermediary metabolite. The Examiner would like to remind the Applicant that claim 119 is drawn to a method using an intermediary metabolite, more specifically, a conjugated biomolecule. Thus, it appears that the Applicant is contradicting the claimed invention.

Claim Rejections - 35 USC § 103-MAINTAINED

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 6, 11, 43-45, 49-52, 59-60, 97, 119, 124 and 161-167 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vliet et al (1999) and Taniguchi.

Vliet et al discloses a method in which NKT B cells isolated from human donors are treated with KRN7000 in culture (see entire document). The alteration in cytokine profiles are shown in Tables 1 and 2 demonstrating both an upregulation and a downregulation of specific NKT cell functions. More specifically, the Table "1 reveal an upregulation of both pro-inflammatory IFN- gamma and anti-inflammatory IL-4 expression, thus, leading to a change in the Thl/Th2 balance

Vliet et al does not teach a method for the treatment of colitis in a mammalian subject with intraperitoneally administration of intermediary metabolites. Taniguchi teaches a method in which NKT cell-activating agents, including galatosylceramides or glucosylceramides, are used for therapeutic agents for diseases, including ulcerative colitis (see whole document, including pages 2 and 3). Further, this prior art reference teaches intraperitoneal administration of intermediary metabolites (see page 9, paragraph 39) comprising glucocerebroside and many of its derivatives (see pages 3-6). It would have been obvious to one of ordinary skill in the art to modify the methods taught by Vliet et al and Taniguchi et al in order to alter the cytokine responses via intraperitoneal administration of an intermediary metabolite to treat mammalian disease.

One would have motivated to do so, given the suggestion by Vliet et al, because KRN7000 can be recognized by NK T-cells and trigger cytokine release and thus, "be a useful agent in the modulation of immune responses" (see Discussion). There would have been a reasonable expectation of success, given the knowledge that intermediary metabolites are already administered for mammialian treatment, for example, the "a-glucosylceramide structure protects the body from radiation" as well as "increases the number of platelets and leukocytes" (Taniguchi et al, see paragraph 8). Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made

In response, Applicants argue that the references are deficient because neither discloses a mammalian intermediary metabolite. As mentioned above, the Examiner will not read limitations into the claims. Further, in contrast to the Applicants' argument, the '906 Application supports "non-mammalian" and "synthetically created" intermediary metabolites. No argument has been found to be persuasive and this rejection is maintained.

Claim 191 is rejected under 35 U.S.C. 103(a) as being unpatentable over Vliet et al (1999), Taniguchi and Connolly and Cunningham (2000). As mentioned above, Vleit et al and Taniguchi combined teach a method for the treatment of colitis in a mammalian subject with intraperitoneally administration of intermediary metabolites. These references do not disclose food and/or water deprivation prior to administration of intermediary metabolites. This practice is, however, commonly taught in the prior art by many references including that by Connolly and Cunningham. It would

have obvious to one of ordinary skill in the art to modify the methods taught by Vliet et al, Taniguchi and Connolly and Cunningham to incorporate fasting prior to the administration of intermediary metabolites. One would have been motivated to do so, given the suggestion by Connolly and Cunningham, in order to minimize the volume and increase the pH of the gastric contents. There would have been a reasonable expectation of success, given this practice has been advised since the late 19th century (see Connolly and Cunningham). Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made

In response, Applicants provide two separate arguments. The first is that the ordinary artisan would not be motivated to incorporate fasting prior to administration of intermediary metabolites. Applicants say nothing more about this particular argument; thus, it is not clear what the point is. Secondly, it is stated that "Applicants require fasting because many foods contain certain amount of various intermediary metabolites that may cause potential unwanted positive and negative effects which would interfere with the desired effect of the treatment". While this may be true as to why the Applicants require fasting prior to administration for their claimed invention, it does not mean that other motivations do not exist. This rejection is maintained.

Double Patenting-MAINTAINED

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct

from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 6, 11, 43-45, 59-60, 97, 119-120, 124-125, 151, 157, 165- 166 and 168-169 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 and 10 of copending Application No. 10/375, 906. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method steps in treating a disease in a mammalian subject are identical.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants failed to respond to the rejection above and therefore, this rejection is maintained.

CONCLUSIONS

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michelle Horning whose telephone number is 571-272-9036. The examiner can normally be reached on Monday-Friday 8:00-5:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michelle Horning
Patent Examiner

BRUCE R. CAMPELL, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Continuation of Disposition of Claims: Claims pending in the application are 1, 6, 11, 43-45, 47-52, 54, 59-60, 75-76, 97, 109, 119-120, 124-126, 151, 157, 161-170, 184, 191 and 205; 2-5, 7-10, 12-42, 46, 53, 55-58, 61-74, 77-96, 98-108, 110-118, 121-123, 129-150, 154-156, 158-160, 171-177, 183, 185, 187, 189, 190, 197, 198 and 200-202.

Form PTO-1449 U.S. Department of Commerce (REV. 8-83) Patent and Trademark Office INFORMATION DISCLOSURE CITATION (use several sheets if necessary)	Atty. Docket No. ENZ-64(CIP)	Serial No. 10/675,980
	Applicants: Ilan, et al	
	Filed: Sep. 30, 2003	Group: 1648

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	FILING DATE IF APPRO-PRIATE

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	TRANS-LATION YES	TRANS-LATION NO
/MH/	WO	9 9 3 3 4 7 5	7/8/99	Fredman, et al	A1			
	EP	0 9 5 7 1 6 1	11/17/99	Koezuka, et al	A1			
	EP	0 9 8 8 8 6 0	3/29/00	Taniguchi, et al	A1			
	WO	0 3 9 3 2 8 7	11/13/03	Vo-Hoang, et al	A1			

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

	Margalit, M., et al., "Glucocerebroside Treatment Ameliorates Con-A Hepatitis by Inhibition of NKT Lymphocytes: A New Immunemodulatory Tool," Hepatology 38:163A (2003)

EXAMINER	/Michelle Horning/	DATE CONSIDERED	07/18/2007

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/MH/	10	3 7 5 9 0 6		Ilan et al			3/4/03
	08	8 0 8 6 2 9		Roy-Chowdhury, et al			2/28/97
		0 1 7 0 2 5 8	2003	Roy-Chowdhury, et al	A1		

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	WO	25 0 5 1 9 8 6	12/24/01	Ilan et al				

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

	Bleicher, P.A., et al., "Expression of murine CD1 on gastrointestinal epithelium," Science 250:679-682 (1990)
	Collins, C., et al., "RAG1, RAG2 and pre-T cell receptor alpha chain expression by adult human hepatic T cells: evidence for extrathymic T cell maturation," Eur. J. Immunol. 26:3114-3118 (1996)
	Madsen, K.L., et al., "Interleukin 10 prevents cytokine-induced disruption of T84 barrier integrity and limits chloride secretion," Gastroenterology 113:151-159 (1997)
	Mitchell, D.G., et al., "Fatty liver. Chemical shift phase-difference and suppression magnetic resonance imaging techniques in animals, phantoms, and humans," Invest. Radiol. 26:1041-1052 (1991)
	Lachman, et al, "Massive hepatic fibrosis in Gaucher's disease: clinico-pathological and radiological features," Q. J. Med 93:237-244 (2000)

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OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

/MH/		Namimoto, T., et al., "Adrenal Masses: Quantification of Fat Content with Double-Echo Chemical Shift In-Phase and Opposed-Phase FLASH MR Images for Differentiation of Adrenal Adenomas," Radiology 218:642-646 (2001)
		Sullards, M.C., et al., "Structure determination of soybean and wheat glucosylceramides by tandem mass spectrometry," J. Mass Spectrometry 35:347-353 (2000)
		Trop, S., et al., "Liver-Associated Lymphocytes Expressing NK1.1 Are Essential for Oral Immune Tolerance Induction in a Murine Model," Hepatology 29:746-755 (1999)
		Vicari, A.P., et al., "Mouse NK1.1 + T cells: a new family of T cells," Immunology Today 17(2):71 (1996)

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